



# Effect of cerebral small vessel disease on cognitive impairment in Parkinson's disease: a systematic review and meta-analysis

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**Background:** The occurrence of various cerebrovascular diseases can easily induce cognitive impairment in the elderly. Therefore, it is of great clinical significance to correctly understand the relationship between these key pathogenic factors and cognitive impairment of Parkinson's disease. To explore the effect of cerebrovascular disease on cognitive impairment in Parkinson's disease by meta-analysis.

**Methods:** PubMed, Medline, Embase, and Web of Science databases were selected as the sources for the literature search. English language articles were included. Literature related to this study were published from January 2001 to January 2021. Literature was screened and the quality was evaluated. RevMan 5.3 software was used to perform the meta-analysis on the effects of cerebrovascular disease on cognitive impairment in Parkinson's disease.

**Results:** Six articles were finally included, involving a total of 5,552 cases. Of these, 2,684 were positive cases, accounting for 48.3%. Compared with patients with non-Parkinson's cognitive impairment, patients with cognitive impairment in Parkinson's disease caused by cerebral small vessel disease had significant differences in executive ability (OR =1.62, 95% CI: 1.21–2.16, P=0.001), memory (OR =1.48, 95% CI: 1.30–1.68, P<0.00001), information processing (OR =0.60, 95% CI: 0.35–1.03, P=0.07), language communication (OR= 4.72, 95% CI: 3.26–6.85, P<0.00001), and overall cognitive function (OR =0.72, 95% CI: 0.52–0.99, P=0.05).

**Conclusions:** A total of 6 studies were included in this meta-analysis on the influence of cerebral small vessel disease on cognitive impairment in Parkinson's disease. This study shows that cerebrovascular disease has different effects on all aspects of cognitive function of Parkinson's disease.

**Keywords:** Cerebral small vessel disease; cognitive impairment; Parkinson's disease; meta-analysis

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## Introduction

With the advent of the aging population, the probability of people suffering from various chronic diseases is also increasing. Among them, the number of clinical cases of Alzheimer's disease, behavioral disorders, and cognitive impairment caused by Parkinson's disease is also increasing year by year (1,2). Cognitive impairment not only poses a huge psychological and physiological burden to patients, but also greatly reduces their quality of life. According to the clinical research results, there are many specific pathogenic factors of cognitive impairment in Parkinson's disease, such as age, disease history, drug history and lifestyle, and there is no unified conclusion (3-5). However, Among these pathogenic factors, cerebral small vessel diseases (6-8), including lacunar cerebral infarction, white matter injury or looseness, cerebral cortex atrophy, cerebral microvascular rupture and enlarged perivascular space, may cause cognitive impairment of Parkinson's disease in elderly patients (see *Figure 1*). At the same time, the he number and location of small cerebrovascular diseases in the basal ganglia may independently lead to gait/posture dysfunction in Parkinson disease patients (9). The effect of small cerebral vessels on Parkinson's cognitive impairment is still in the exploratory stage. Therefore, it is of great clinical significance to understand the relationship between these key pathogenic factors and cognitive impairment in Parkinson's disease, this is the innovation and significance of this work. In this study, meta-analysis was used to further explore the effect of small vessel disease on cognitive impairment in Parkinson's disease. We present the following article in accordance with the MOOSE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-276/rc>).

## Methods

### *Data sources and search strategy*

PubMed, Medline, Embase, and Web of Science literature databases were used in this study. When conducting literature retrieval, the language of publications was limited to English, and the publication time was limited from 2001 to 2021. The literature retrieval methods involved rapid retrieval of English words and combinatorial retrieval of literature keywords. The search keywords were "cerebrovascular disease", "Parkinson's disease", "effect", and "cognitive impairment". The full-text searches of the database were carried out through free combinations of these keywords. At the same time, the relevant citations

were tracked by manual retrieval. The retrieval time was October 21, 2021.

### *Inclusion criteria*

The inclusion criteria were as follows: (I) the included studies were case-control studies on the correlation between cerebrovascular diseases and cognitive function in Parkinson's disease; (II) data related to the evaluation of cognitive impairment was complete.

### *Exclusion criteria*

The exclusion criteria were as follows: (I) the subjects were patients with acute stroke or dementia; (II) subjects were complicated with infection, epilepsy, tumor, multiple sclerosis, or psychosis, which could potentially affect cognitive function; (III) incomplete data or logical error; (IV) only no repeatedly published data was used as a reference.

### *Selection of literature*

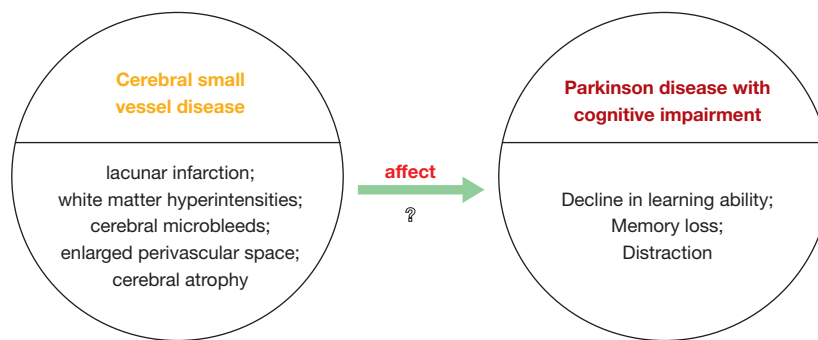
Literature was screened by 2 independent researchers. All titles were first read and compared by these 2 researchers. Then, ineligible publications were excluded, while eligible publications were obtained and fully read by these 2 researchers. The 2 researchers performed cross-checking to exclude uncertain papers. Finally, a third person was introduced to assist in arbitration.

### *Data extraction*

Two researchers independently extracted the relevant data and information for this study, including the first author, the time of publication, the number of patients with cerebrovascular diseases and controls, the average age and sex ratio of the subjects. All data in this study were extracted and analyzed independently by 2 authors. In case of divergent opinions, a comprehensive evaluation was conducted by a third party.

### *Literature quality assessment*

The Newcastle Ottawa Scale (NOS) was used to evaluate the quality of the included studies. NOS is a commonly used quality evaluation in case-control studies and cohort studies. It should be noted that NOS is a continuous cooperation



**Figure 1** The possible effects of cerebral small vessel disease on cognitive impairment in Parkinson's disease.

project. The purpose of this project is to provide a simple and convenient quality assessment tool for the inclusion of non-randomized studies in the systematic review. The score of the scale, and the full score is 9 points. The evaluation items mainly include three items: object selection, comparability, outcome (cohort study) or exposure (case-control). There are evaluation items under each item, and each item is represented by scores when appropriate. The highest score of comparability is 2 points. At present, NOS scale has been widely used to evaluate case-control studies and cohort studies. Five articles scored 6, 1 article scored 7, and 1 article scored 5, indicating good quality. The higher the score, the better the literature quality and the lower the bias.

### Statistical analysis

Meta-analysis was conducted using RevMan 5.3 software provided by the Cochrane Collaboration Network. Heterogeneity was tested by the Q test, where  $P > 0.1$  and  $I^2 < 50\%$  indicated that the homogeneity among the studies was good, and the fixed effect model was used. When  $P \leq 0.1$  or  $I^2 \geq 50\%$ , the heterogeneity among the groups was large, and the random effect model was used. If the heterogeneity was too large, subgroup analysis was carried out ( $P > 0.1$  and  $I^2 < 50\%$ ).  $P < 0.1$  was considered statistically significant for all the above effect analyses.

## Results

### Literature search and screening results

In this study, 615 relevant publications were initially found. First, records removed before screening: duplicate records removed ( $n=132$ ), records marked as ineligible by automation tools ( $n=87$ ), records removed for other

reasons ( $n=34$ ). Then 335 articles were filtered out by records screen the remaining 27 articles were included in the primary screening, and finally 6 studies were included involving a total of 5,552 cases (Figure 2). Of these cases, 2,684 were positive cases, accounting for 48.3%. The basic characteristics of the studies are shown in Table 1, while the reasons for literature exclusion are shown in Table 2.

### Literature quality evaluation

According to our retrieval strategy, literature retrieval was implemented, and finally 6 studies were included in this meta-analysis. A total of 5,552 patients were included in these 6 studies. Among them, patients with cerebrovascular diseases were included in the study group and were compared to patients in the control group. The basic characteristics and NOS scores of the included studies are shown in Table 1.

### Meta-analysis results

#### Executive ability

Five studies (5,10-13) reported the effects of cerebrovascular diseases on the executive ability of patients with cognitive impairment in Parkinson's disease, including 3,085 patients with executive dysfunction in Parkinson's disease and 2,367 patients with executive dysfunction in non-Parkinson's disease. There was no heterogeneity between the studies ( $I^2=46\%$ ,  $P=0.12$ ). Fixed effect model analysis showed that compared with the executive dysfunction of patients with non-Parkinson's disease, the executive ability was a significant difference in patients with Parkinson's disease and executive dysfunction caused by cerebral small vessel disease (OR =1.62, 95% CI: 1.21–2.16,  $P=0.001$ ), as shown in Figure 3.

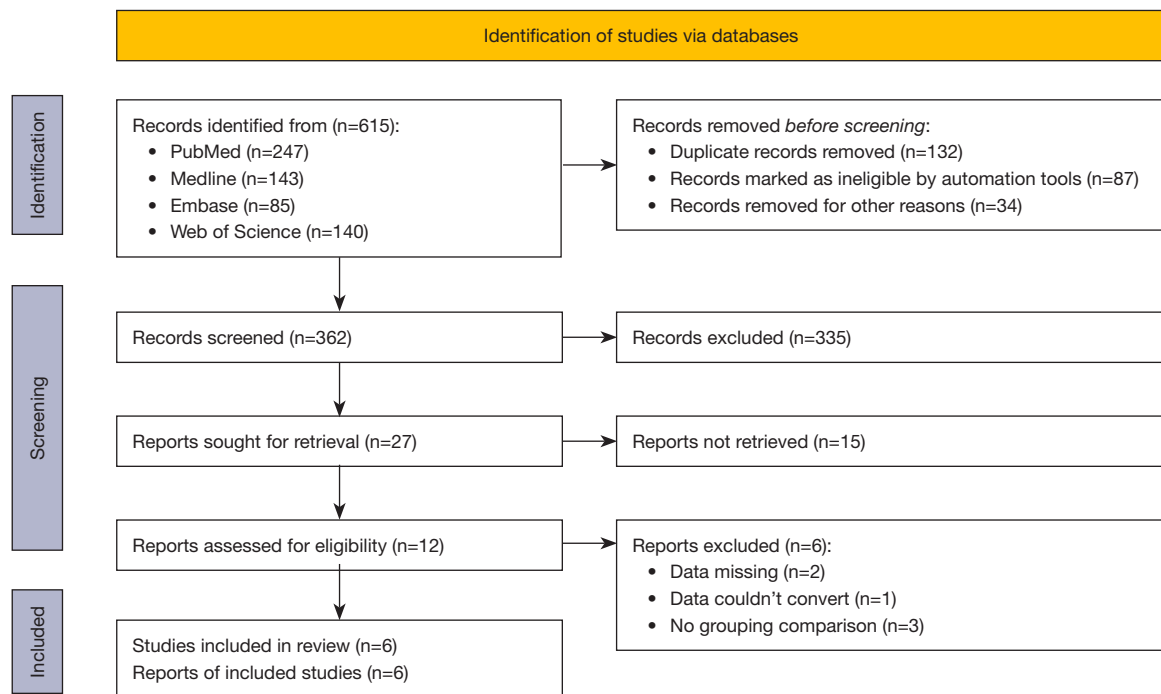


Figure 2 Search and selection flow chart of literature.

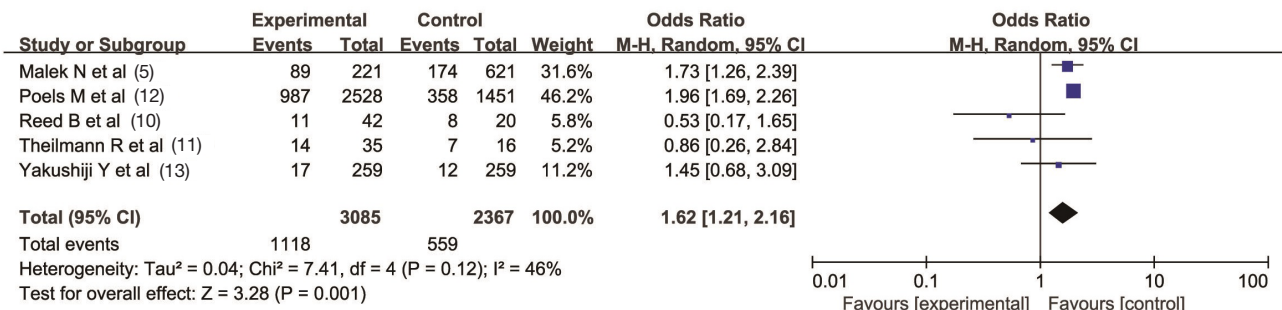
Table 1 Summary of the basic characteristics of the studies and areas of cognitive impairment affected

Serial number	Author	Study location	Year of publication	Total cases	Impact indicators	Quality score (points)
1	Malek N <i>et al.</i> (5)	Glasgow, Kingdom	2016	1759	(I)(II)(III)(V)	4
2	Reed BR <i>et al.</i> (10)	Martinez	2004	62	(I)(II)(III)(V)	4
3	Theilmann RJ <i>et al.</i> (11)	San Diego, USA	2013	51	(I)(II)(IV)(V)(VI) (VII)(VIII)(IX)	8
4	Poels MM <i>et al.</i> (12)	Rotterdam	2012	3979	(I)(II)(IV)	3
5	Yakushiji Y <i>et al.</i> (13)	Saga, Japan	2008	518	(I)(II)(IV)	3
6	MacLulich AM <i>et al.</i> (14)	France	2004	100	(V)	1

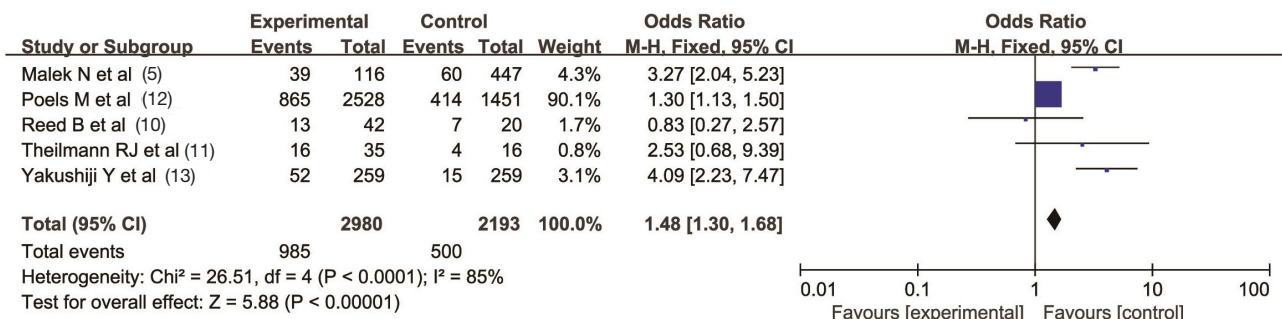
(I) executive ability; (II) memory; (III) information processing; (IV) language communication; (V) overall cognitive function; (VI) learning ability; (VII) visual space perception; (VIII) attention; (IX) language fluency.

Table 2 Excluded literature and reasons for exclusion (not all)

Serial number	Author	Year of publication	Reason for exclusion
1	Rensma SP <i>et al.</i> (15)	2018	Not enough data
2	Wan Y <i>et al.</i> (16)	2019	Not enough data
3	Foo H <i>et al.</i> (17)	2016	No group comparison data
4	Ma X <i>et al.</i> (18)	2021	Not enough data



**Figure 3** Effect of cerebrovascular disease on executive ability in Parkinson's disease.



**Figure 4** Effect of cerebrovascular disease on memory in Parkinson's disease.

## Memory

Five studies (5,10-13) reported the effects of cerebrovascular diseases on memory in Parkinson's disease patients with cognitive impairment, including 2,980 patients with memory impairment in Parkinson's disease and 2,193 patients with memory impairment in non-Parkinson's disease. There was heterogeneity among the studies ( $I^2=85\%$ ,  $P<0.0001$ ). Random effect model analysis showed that compared with patients with memory impairment in non-Parkinson's disease, there was a significant difference in patients with memory impairment in Parkinson's disease caused by cerebral small vessel disease (OR =1.48, 95% CI: 1.30–1.68,  $P<0.00001$ ), as shown in *Figure 4*.

## Information processing

Two studies (5,10) reported the impact of cerebrovascular diseases on information processing in Parkinson's disease, including 163 patients with information processing disorder in Parkinson's disease and 120 patients with information processing disorder in non-Parkinson's disease. There was

no heterogeneity between the studies ( $I^2=0\%$ ,  $P=0.36$ ). Fixed effect model analysis showed that compared with non-Parkinson's disease patients with information processing disorder, there was a significant difference in Parkinson's disease patients with information processing disorder caused by cerebral small vessel disease (OR =0.60, 95% CI: 0.35–1.03,  $P=0.07$ ), as shown in *Figure 5*.

## Language communication

Three studies (11-13) reported the effects of cerebrovascular diseases on language communication in Parkinson's disease, including 1,152 patients with language communication disorder in Parkinson's disease and 957 patients with language communication disorder in non-Parkinson's disease. There was heterogeneity among the studies ( $I^2=67\%$ ,  $P=0.05$ ). Random effect model analysis showed that compared with non-Parkinson's disease patients with language communication disorder, there was a significant difference in Parkinson's disease patients with language communication disorder caused by cerebral small vessel



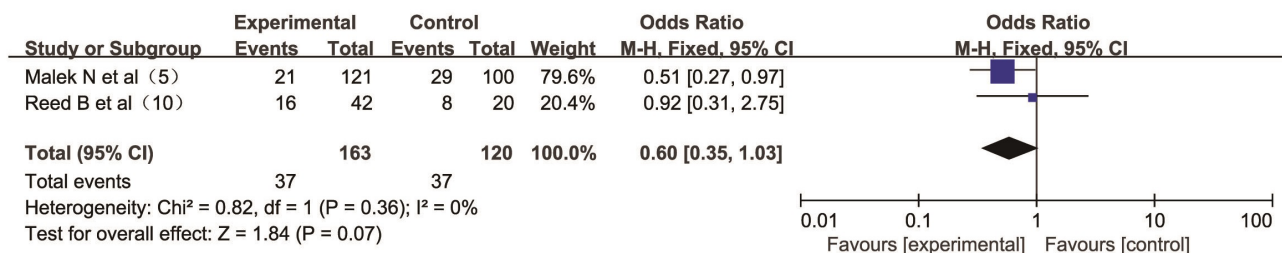


Figure 5 Effect of cerebrovascular disease on information processing in Parkinson’s disease.

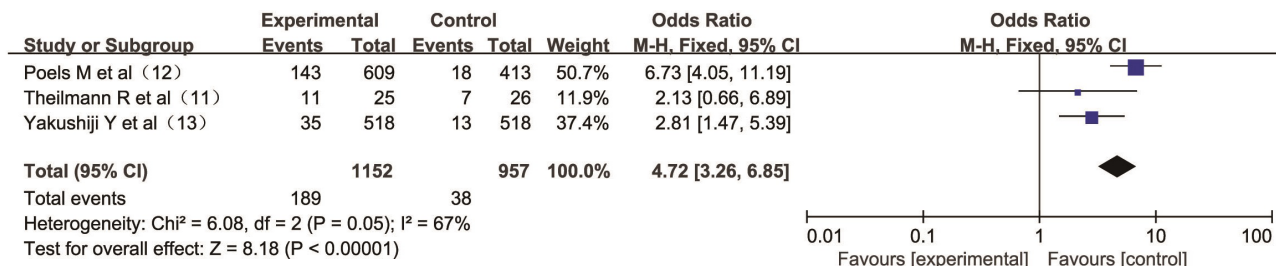


Figure 6 Effect of cerebrovascular disease on language communication in Parkinson’s disease.

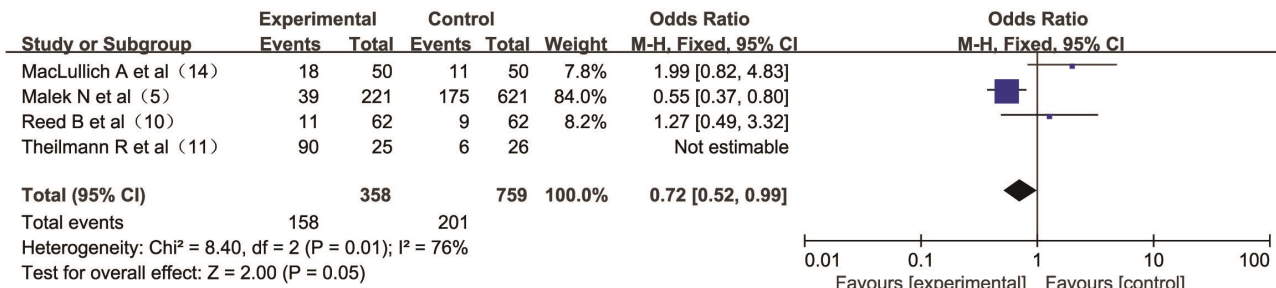


Figure 7 Effect of cerebrovascular disease on overall cognitive impairment in Parkinson’s disease.

disease (OR =4.72, 95% CI: 3.26–6.85, P<0.00001), as shown in *Figure 6*.

**Overall cognitive impairment**

Four studies (5,10,11,14) reported the effect of cerebrovascular diseases on overall cognitive impairment in Parkinson’s disease, including 358 patients with overall cognitive impairment in Parkinson’s disease and 759 patients with overall cognitive impairment in non-Parkinson’s disease. There was heterogeneity among the studies (I<sup>2</sup>=76%, P=0.01). Random effect model analysis showed that compared with patients with overall cognitive impairment in non-Parkinson’s disease, patients with overall cognitive

impairment in Parkinson’s disease caused by cerebral small vessel disease had a significant difference (OR =0.72, 95% CI: 0.52–0.99, P=0.05), as shown in *Figure 7*.

**Analysis of publication bias**

Publication bias analysis was not performed as few articles were included in this study.

**Discussion**

Cognitive impairment is the most common non-motor symptom in Parkinson’s disease. It can be divided into mild cognitive impairment and dementia according to

the severity of the disease. Mild cognitive impairment in Parkinson's disease is a risk factor for the development of Parkinson's dementia. At present, this type of cognitive impairment accounts for about 30% of patients with Parkinson's disease cognitive impairment, and most of them are non-forgetting. The predominant clinical manifestations are reduced learning ability, memory function, and inattentiveness. At present, the pathogenesis of cognitive impairment in Parkinson's disease is not clear, but most scholars generally believe that it is mainly related to brain beta amyloid protein deposition and microvascular disease caused by pathological mechanisms such as oxidative stress, brain mitochondrial function damage, and changes in various neurotransmitters in the nervous system (19). At the same time, according to the results of relevant clinical studies, baseline orthostatic hypotension and autonomic nerve dysfunction in patients with early Parkinson's disease are related to the mediating effect of cerebrovascular disease and the decline of cognitive ability in the later stage (20-23).

The occurrence of cerebral small vessel disease is usually caused by 2 main factors, namely amyloidosis of cerebral white matter and hypertension (24). According to the research conclusions of Hachinski *et al.* (25) and other research groups, cerebral small vessel hemorrhage caused by cerebral white matter amyloidosis mainly forms blood foci in the cerebral lobes, while cerebral small vessel hemorrhage caused by hypertension mainly occurs in the deep part of the brain, such as the thalamus and basal ganglia. In addition, according to the meta-analysis results of Wu *et al.* (26), damage to the deep brain, lateral lobe, basal ganglia, and hypothalamus will affect the cognitive function of patients to varying degrees. In addition to cognitive function, there is a close relationship between cerebral small vessel diseases and motor symptoms. It is found by clinical research that the hyperintensity of deep white matter in the middle frontal lobe is a risk factor for postural instability and gait disorder, which supports the contribution of vascular pathology of Parkinson's disease (16).

Cognitive impairment and dementia are recognized as the consequences of the neurodegenerative process of Parkinson's disease. Patients will not only show abnormalities in executive function, memory, language, attention, visual space and other fields, but also affect their quality of life and prognosis to varying degrees. Although the research on phobia with cognitive impairment and cerebrovascular disease is gradually increasing, its pathological mechanism is not clear, and there are few clinical research reports on whether the intervention of

cerebrovascular disease is conducive to improving the symptoms of Parkinson's cognitive impairment and delaying the progress of the disease. Therefore, in the future, large-scale prospective studies and relevant basic experiments need to be improved to clarify the relationship and specific mechanism between cerebrovascular disease and Parkinson's cognitive impairment, so as to provide clues and ideas for the diagnosis, treatment and prognosis of Parkinson's patients (27,28).

In this study, the effects of cognitive impairment in Parkinson's disease caused by cerebrovascular disease were analyzed by meta-analysis. Compared with patients with non-Parkinson's disease, patients with Parkinson's disease cognitive impairment caused by cerebral small vessel disease were significantly different in terms of executive ability, memory, information processing, language communication, and overall cognitive function ( $P < 0.01$ ). Therefore, these data show that cerebral small vessel disease has different effects on all aspects of cognitive function of Parkinson's disease.

## Conclusions

In conclusion, cognitive impairment is the main result of neurodegenerative diseases and the continuous progression of Parkinson's disease. Because patients are significantly lower than healthy people in terms of executive ability, memory function, language expression, and attention and visual space perception, their quality of life is seriously affected. Although there are more and more reports on the impact of cerebrovascular disease on cognitive impairment in Parkinson's disease, the research on its specific pathogenesis has not been systematic. Therefore, through the retrieval of relevant literature and meta-analysis of the existing research, we revealed the relationship between these conditions and the specific impact of cerebrovascular disease. These findings have guiding significance and clinical reference value for the diagnosis, treatment, and prognostic improvement of patients with Parkinson's disease cognitive impairment.

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## Footnote

*Reporting Checklist:* The authors have completed the MOOSE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-276/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-276/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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